REMARKS

This Application has been carefully reviewed in light of the Office Action mailed February 3, 2005. At the time of the Office Action, Claims 138-148 were pending in this Application. Claims 138-148 were rejected. Claims 149-151 were previously cancelled without prejudice or disclaimer. Claim 146 has been amended herein to correct an inadvertent typographical error. Applicant respectfully requests reconsideration and favorable action in this case.

Applicant has amended the specification herein. Applicant asserts that it would have been obvious to one of ordinary skill in the art that simple misspellings of the intended compound names appeared in the specification and claims as originally filed. In some cases, the corrections made herein simply replace the numeral "1" (one) with the letter "l," for example, in the formula "HCl." In other cases, the hydrochloride form of a drug was indicated with a period (*e.g.*, isoxsuprine.HCl) and is herein corrected to a hyphen or dot (*e.g.*, isoxsuprine HCl). In still others, omitted, transposed, and incorrect letters are corrected. In each case, Applicant contends that one of ordinary skill in the art would have been able to identify the intended compound name from the misspelled name. Support for some of the amendments may be found in the specification as originally filed at, for example, page 25, line 13 to page 27, line 9.

In one case, an abbreviation, "DTC," is spelled out as "dacarbazine." Applicant respectfully asserts that the identity of DTC as dacarbazine would have been apparent one of ordinary skill in the art since, for example, Bayer sells dacarbazine under the trade name "DTC-Dome."

With regard to the amendments to Examples VIII, XI, XII, and XIV, Applicant asserts that these amendments are fully supported by the application as filed.

Specification Objections

The Specification was objected to under 35 U.S.C. §132 because it allegedly introduces new matter into the disclosure.

With regard to the amendments to Examples VIII, IX, and X replacing bismuth citrate with bismuth sulfate, Applicant respectfully observes that the opening paragraph of the section at Page 53, Lines 2-5 explicitly states:

> The formulations of Examples VIII, IX, and X include **bismuth sulfate**. In each of these examples, solution dosage forms were

prepared by adding an amount of an ammonium salt of **bismuth sulfate** sufficient to provide **the indicated amount** of **bismuth sulfate**.

Therefore, one would logically expect each of the named examples to recite an "amount of bismuth sulfate" as this paragraph indicates. In addition, Applicant respectfully invites the Examiner's attention to the paragraph following each formulation of Examples IX and X, wherein the text recites "to the resulting clear solution were added the bismuth sulfate and ... water." See e.g. Page 53, Lines 12-13. Moreover, the orderly arrangement and flow of the application with Examples VIII through XII disclosing bismuth sulfate and Examples XIII through XVI disclosing bismuth citrate further indicates that the formula disclosed in each of examples VIII through XII should recite bismuth sulfate. Since they instead recite bismuth citrate to the exclusion of bismuth sulfate, it is apparent that "citrate" was inadvertently substituted for "sulfate" in Examples VIII, IX, and X. Accordingly, Applicant respectfully requests withdrawal of this objection.

With regard to the objection to the use of the phrase "aqueous soluble" in connection with the bismuth compound, Applicant respectfully disagrees and asserts that this phrase is fully supported. Indeed, the application as originally filed is replete with disclosures of aqueous solutions comprising dissolved bismuth including the very Example where this phrase is to be inserted. Accordingly, Applicant respectfully requests withdrawal of this objection.

Regarding the remaining objections, Applicant respectfully invites the Examiner's attention th the amendments made herein to restore the text to its original form. In so doing, Applicant does not concede the accuracy or reasonableness of the objections or that artisans of ordinary skill would not agree with Applicant's position. Specifically, the invention contemplates the use of a variety of bismuth compositions and need not be confined to bismuth compositions having the coordinated structure of a chelate. Accordingly, Applicant simply notes that the objection is now moot in view of the specification amendments made herein.

Rejections under 35 U.S.C. § 112

Claims 145-147 were rejected by the Examiner under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement. Applicant traverses this rejection and respectfully asserts that a number of compounds with each of the recited properties have been provided in the specification as originally filed, for example, at Page 25,

Line 13 to Page 27, Line 9. Examples of agents with anticonvulsant activity include any of the disclosed anti-asthma compounds disclosed such as albuterol sulfate. Examples of agents capable of prolonging survival under hypoxic conditions include any of the vasodilators (e.g. hydrazine, isoxsuprine, nylidrin) or bronciodilators (*e.g.*, dyphylline, pirbuterol, colfosceril palmitate). Examples of agents capable of alleviating or ameliorating a condition selected from the group consisting of stomatitis, gingivoglossitis and toothache include any of the antiviral compounds disclosed, particularly those with anti-hepatitis activity (*e.g.*, acyclovir, interferon, penciclovir). Accordingly, Applicant respectfully requests withdrawl of this rejection.

Claims 138-148 were rejected by the Examiner under 35 U.S.C. §112, second paragraph, as being allegedly indefinite and failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. According to the Office Action, the term "clear" allegedly does not provide a standard for ascertaining the requisite degree of clearness or transparency.

Applicant traverses this rejection and respectfully asserts that one of ordinary skill in the art would have been reasonably apprised of the metes and bounds of the claimed invention. For example, Applicant respectfully invites the Examiner's attention to the specification at page 19, lines 9-10, wherein Applicant has disclosed that:

> These aqueous solution systems of bile acids are **substantially free of precipitate or particles**. A further advantage of this invention is that the aqueous solution systems demonstrate **no changes** in physical appearance such as changes in **clarity**, color or odor following the addition of strong acids or alkali even after several months observation under accelerated conditions of storage at 50° C.

The Examiner's attention is also respectfully invited to paragraph 9 of the Rule132 Declaration enclosed herewith. Therefore, since the term "clear" is clear and definite, Applicant respectfully request withdrawal of this rejection.

Rejections under 35 U.S.C. § 102

Nakazawa Is Unavailable as Prior Art

Claims 138-141 were rejected by the Examiner under 35 U.S.C. §102(b) as being anticipated by Japanese Patent Application Publication No. 62153220 by Shinzo Nakazawa

and Satoshi Hisano (previously identified as "Satoshi," but hereafter, "Nakazawa"). Applicant respectfully traverses and submits the cited art does not teach all of the elements of the claimed embodiment of the invention.

In order for a reference to anticipate, it must provide an enabling disclosure. See e.g., MPEP § 2121.01. Accordingly, in order to be available as prior art to the instant disclosure, it must provide an enabling disclosure of each and every element of the claimed invention. However, as the Rule 132 Declaration submitted previously demonstrated, the disclosures of Nakazawa, when followed, did not result in the production of a stable, clear solution. However, according to the present Office Action, the experimental results presented therein actually provided objective evidence that the solutions of Nakazawa are "clear."

Applicant respectfully disagrees and asserts that nowhere does Applicant's prior Declaration demonstrate or concede that Nakazawa enables formation of clear aqueous solutions of bile acids. In every instance where the earlier Declaration refers to the Nakazawa compositions as "clear," the Declaration plainly indicates that it is the supernatant that is clear, and that only after substantial precipitate has had time to settle out. *See e.g.*, May 14, 2004 Declaration, Paragraph 6(A)(i). In another example, a Nakazawa solution was described as lacking the initial turbidity observed with other Nakazawa solutions. *See* May 14, 2004 Declaration, Paragraph 6(A)(ii). However, in this case, the composition is still described as being "mostly clear with some undissolved matter." Accordingly, it cannot be said that it was substantially free of precipitate or particulate.

According to the Office Action, visual assessment of clarity is called into question as possibly involving a degree of subjectivity. The Examiner suggests that a practitioner may ask whether a "clear" solution may also be "milky," "opalescent" or "turbid." The Examiner continued, stating that the pending claims "do not recite a range for the quality of being clear, *i.e.*, absorbance." According to the Office Action, this makes it difficult to interpret the data presented in the earlier Declaration.

Applicant respectfully traverses these allegations and, in response, encloses herewith a second Rule 132 Declaration providing nearly exhaustive data regarding the compositions of Nakazawa as well as absorbance data for several compositions of the disclosure. Consistent with the data presented in the earlier disclosure, the Rule 132 Declaration enclosed herewith demonstrates that the compositions of Satoshi are very plainly not clear. Accordingly, Applicant again asserts that Nakazawa is not available as prior art against the instant application and respectfully requests withdrawal of this rejection.

Pending Claims Are Patentable over Panini, Widauer, and

Claims 138-141 were rejected by the Examiner under 35 U.S.C. §102(b) as being anticipated by *Improvement of Ursodeoxycholic Acid Bioavailability by 2-Hydroxypropyl-β-Cyclodextrin Complexation in Healthy Volunteers*, by R. Panini et al., Pharmacological Research, Vol. 31, No. 3/4, 1995 ("Panini et al."). Applicant respectfully traverses and submits the cited art does not teach all of the elements of the claimed embodiment of the invention.

Claims 138-141 were rejected by the Examiner under 35 U.S.C. §102(b) as being anticipated by U.S. Patent No. 5,534,505 issued to Josef O. Widauer ("Widauer"). Applicant respectfully traverses and submits the cited art does not teach all of the elements of the claimed embodiment of the invention.

Claims 138-141 were rejected by the Examiner under 35 U.S.C. §102(b) as being anticipated by *Improvement of Water Solubility and Dissolution Rate of Ursodeoxycholic acid and Chenodeoxycholic acid by Complexation with Natural and Modified β-cyclodextrins*, by C.A. Ventura et al., International Journal of Pharmaceutics, Vol. 149, pp. 1-13, 1997 ("Ventura et al."). Applicant respectfully traverses and submits the cited art does not teach all of the elements of the claimed embodiment of the invention.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1997). Furthermore, "the identical invention must be shown in as complete detail as is contained in the ... claim." *Richardson v. Suzuki Motor Co. Ltd.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). Applicant respectfully submits that the cited art as anticipatory by the Examiner cannot anticipate the rejected Claims, because the cited art does not show all the elements of the present Claims.

There are at least three substantial differences between Widauer and the instant claims. First, Widauer fails to teach a clear aqueous solution, but instead teaches a solution in which most of the UDCA is in the form of crystalline particles. *See e.g.* Widauer, col. 1, lines 62-67 ("...contains the active agent [UDCA] **mainly** in a fine crystalline form...")(emphasis added). In fact, Widauer teaches that the amount of soluble UDCA should be kept to a minimum to eliminate the bitter taste of naturally dissolved UDCA. *See* Widauer, col. 2, lines 12-17.

Second, the end product taught by Widauer is very different from the instant invention. The UDCA that is present in the compositions of Widauer exists as an inclusion product, bound in the hydrophobic pocket of cyclodextrin by hydrophobic interactions. *See e.g.* Widauer, col. 2, lines 45-47. Without being limited to any particular mechanism, it is believed that the solubilized UDCA in compositions of the invention interacts with the solvation milieu principally through hydrogen bonding and ionic interactions. Moreover, unlike some solutions of the present invention, the solution of Widauer lacks a bitter bile taste. This bitter taste is further evidence of the chemical difference between the inclusion product of Widauer and the hydrogen-bonded product of the instant invention. (Naturally, Applicant contemplates and does not wish to surrender the possibility of adding taste masking materials to compositions of the invention.)

Third, β-cyclodextrin is not an aqueous-soluble starch conversion product according to the invention. Applicant respectfully invites the Examiner's attention to the instant application at Page 22, Line 3 *et seq.*, wherein several characteristics are listed that exclude cyclodextrins. For example, the specification discloses that aqueous soluble starch conversion products are formed by partial or complete hydrolysis of starch. *See* Page 22, Lines 7-8. Thus, water-soluble starch conversion products of the invention are those that result only from hydrolysis of starch. By contrast, β-cyclodextrin is synthesized by bacteria (*e.g. Bacillus macerans*) in a two step process. First, a linear heptameric D-glucopyranose is hydrolyzed from starch, *e.g.* amylose. Second, the heptamer is cyclized in a transglycosylation reaction. *See e.g.* Widauer, col. 2, lines 39-42. This second step does not proceed by a hydrolytic mechanism that requires water as a reactant, but rather, it involves the removal of a water molecule (dehydration). Water is a <u>product</u> of the reaction, <u>not</u> a reactant.

In addition, the disclosure states that if the aqueous soluble starch conversion product is polymeric, "the polymer has at least one reducing end and at least one non-reducing end." *See* Page 22, Lines 17-18. Therefore, an "aqueous soluble starch conversion product," as defined in the specification, cannot be interpreted to include cyclodextrins. Accordingly, Panini, Widauer, and Ventura fail to teach an "aqueous soluble starch conversion product" as claimed. Applicant respectfully requests withdrawal of this rejection.

Rejections under 35 U.S.C. §103

Claims 138-147 were rejected under 35 U.S.C. §103(a) as being unpatentable over Nakazawa and U.S. Patent No. 6,210,699 issued to Ramesh N. Acharya et al. ("Acharya et al."). Applicant respectfully traverses and submits the cited art combinations, even if proper, which Applicant does not concede, does not render the claimed embodiment of the invention obvious.

Claim 148 was rejected under 35 U.S.C. §103(a) as being unpatentable over Nakazawa and *2-Hydroxypropyl-β-Cyclodextrin Complexation with Ursodeoxycholic Acid*, by M.A. Vandelli et al., International Journal of Pharmaceutics, Vol. 118, pp. 77-83, 1995 ("Vandelli et al."). Applicant respectfully traverses and submits the cited art combinations, even if proper, which Applicant does not concede, does not render the claimed embodiment of the invention obvious.

In order to establish a *prima facie* case of obviousness, the references cited by the Examiner must disclose all claimed limitations. *In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (C.C.P.A. 1974). Furthermore, according to § 2143 of the Manual of Patent Examining Procedure, to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991).

As already discussed above, since Nakazawa fails to enable clear aqueous solutions, it is unavailable as prior art against the instant claims. Contrary to the allegations in the outstanding Office Action, the distinctive feature, namely clarity, is adequately included in the claims by recitation of the term "clear." Acharya and Vandelli, whether considered alone or in combination, fail to teach or suggest every element of the claimed compositions.

CONCLUSION

Applicant has now made an earnest effort to place this case in condition for allowance in light of the amendments and remarks set forth above. Applicant respectfully requests reconsideration of Claims 138-148.

Applicant encloses a check in the amount of $ 510.00 for the Petition for Extension of Time. Applicant believes there are no further fees due at this time, however, the Commissioner is hereby authorized to charge any additional fees necessary or credit any overpayment to Deposit Account No. 02-4377 of Baker Botts L.L.P.

If there are any matters concerning this Application that may be cleared up in a telephone conversation, please contact Applicant's attorney at (512) 322-2647.

Respectfully submitted,
BAKER BOTTS, L.L.P.

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Neil P. Sirota
PTO Reg. No. 38,306

Guy F. Birkenmeier
PTO Reg. No. 52,622
Attorneys for Applicant

BAKER BOTTS, L.L.P.
30 Rockefeller Plaza
New York, NY 10112
(212) 408-2500